

**IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF NEW JERSEY**

**IN RE BENICAR (OLMESARTAN)  
PRODUCTS LIABILITY  
LITIGATION**

**MDL No. 2606**

Master Case No. 15-2606 (RBK/JS)

Hon. Robert B. Kugler, U.S.D.J.

Hon. Joel Schneider, U.S.M.J.

THIS DOCUMENT RELATES TO  
ALL CASES

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**DEFENDANTS' BRIEF IN SUPPORT OF MOTION TO EXCLUDE THE  
TESTIMONY OF PLAINTIFFS' EXPERT STEPHEN LAGANA, M.D.**

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DRINKER BIDDLE & REATH LLP  
*A Delaware Limited Liability Partnership*  
600 Campus Drive  
Florham Park, New Jersey 07932-1047  
(973) 549-7000  
Attorneys for Defendants Daiichi Sankyo,  
Inc., Daiichi Sankyo US Holdings, Inc.,  
Daiichi Sankyo Company, Ltd., Forest  
Laboratories, Inc., now known as Forest  
Laboratories, LLC, Forest Pharmaceuticals,  
Inc., and Forest Research Institute, Inc.

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### **PRELIMINARY STATEMENT**

Plaintiffs proffer Dr. Stephen Lagana, a pathologist, for the general causation opinion that olmesartan medications can cause sprue-like enteropathy. His opinion should be excluded. First, as a threshold matter, there are three major flaws with his opinion right out of the gate: 1) Dr. Lagana cannot provide any type of specific definition of the sprue-like enteropathy he associates with olmesartan; 2) he cannot define criteria for a pathological diagnosis of this sprue-like enteropathy; and 3) he cannot define general causation. This alone is sufficient to wipe out his general causation opinion under *Daubert*.

Second, and equally fatal to his proffered opinion under *Daubert*, Dr. Lagana did not apply the correct scientific methodology in reaching his opinion. He failed to apply the requisite Bradford-Hill criteria, and could not explain his failure to do so. Analysis of the Bradford-Hill criteria is the scientifically sound methodology for determining general causation; failure to use it is fatal to a general causation opinion. And so it is here.

### **STATEMENT OF FACTS**

As is the case with plaintiffs' experts Drs. Lebwohl and Leffler, there are no limits to Dr. Lagana's "definition" of the sprue-like enteropathy he associates with olmesartan. He just cannot define the condition with any specificity: it is instead any gastrointestinal problem in a patient on an olmesartan medicine that improves to some subjective degree over an undefined period of time after olmesartan is discontinued. Certification of Daniel B. Carroll, Esq. ("Carroll Cert."), Exhibit A, Deposition of Stephen Lagana, M.D. ("Lagana Dep.") at T73:3-T77:19. There is no cardinal finding that can establish the diagnosis. *Id.* at T:232:11-17. And Dr. Lagana would defer to a gastroenterologist to answer the question of what degree of clinical improvement is needed before concluding there has been a successful dechallenge (cessation of the medication). *Id.* at T198:8-20. Moreover, Dr. Lagana testified that he need *not* rule out other explanations for enteropathy, such as co-morbidities or use of other drugs, before diagnosing the sprue-like enteropathy he associates with olmesartan. *Id.* at T177:16-19.

When asked to identify the pathologic criteria that need to be met before diagnosing sprue-like enteropathy associated with olmesartan use, Dr. Lagana skirted specifics. He instead responded that it is a "clinicopathologic diagnosis, so showing me a slide in a vacuum, I can't give you that diagnosis. I can raise that as a possibility and then in following up with the clinical information, certainly I can

get there as the most likely cause of the pattern of injury.” Carroll Cert., Exhibit A, Lagana Dep. at T59:13-24, T60:1-4. Speculative possibilities are not enough to establish general causation.

In addition to having a borderless concept of olmesartan-related sprue-like enteropathy, Dr. Lagana could not provide a specific definition of general causation: “Well, I would say causation or general causation refers to, if a stimulus leads to an event, that would be causation, and in medicine, we apply the reasonable medical threshold, which means more likely than not.” *Id.* at T20:19-T21:3. As established below, this is not even close to meeting the definition of science-based general disease causation.

In fact, when asked whether olmesartan has been proven by reliable, methodologically sound evidence as a cause of sprue-like enteropathy in the general population, Dr. Lagana said the term “general population” was “throwing me a little bit in this context, because we know certainly plenty of people take olmesartan and do not have sprue-like enteropathy, so there is likely cofactors that are still being determined. They may be genetic.” *Id.* at T23:9-T24:6.

When asked about the methods he used in reaching his opinion on general causation, Dr. Lagana replied that he reviews peer-reviewed, published literature, applies his experience with “various entities” and discussed “new entities” with

colleagues and experts. Carroll Cert., Exhibit A, Lagana Dep. at T209:11-24, T210:1-6. This is his methodology.

While he testified that he was aware of the Bradford-Hill criteria, he could not explain why he did not analyze them: “I think it influences my thinking, those points influence my thinking. I didn’t explicitly go through them because – I don’t know. Just did not do that.” *Id.* at T357:5-24. When later questioned by plaintiffs’ counsel in an effort to undo this damaging testimony, Dr. Lagana could only state that he “did think about them and I did address them, although not in the context of listing the criteria point – on a point by point basis.” *Id.* at T406:2-20.

Dr. Lagana’s failure to apply the Bradford-Hill criteria means that he did not consider epidemiology, consistency, dose response, or specificity as part of his methodology in reaching his general causation opinion. Without appropriate methodology, his opinion fails and must be excluded.

### **LEGAL ARGUMENT**

#### **I. DR. LAGANA’S OPINION IS NOT BASED ON A SOUND SCIENTIFIC METHODOLOGY AND SHOULD THEREFORE BE EXCLUDED.**

In determining whether an expert’s general causation opinion is based on a sound, scientific, and thus reliable methodology as to disease causation, the Court must look to various factors: (1) whether the expert relied on epidemiological studies; (2) whether the expert ignored or sufficiently addressed epidemiological

studies which contradicted his hypothesis, explaining the discrepancy between his hypothesis and that of the authors; (3) whether the findings set forth in the studies are statistically significant.” *Pritchard v. Dow Agro Sciences*, 705 F. Supp. 2d 471, 484-85 (W.D. Pa. 2010) (relying on *Heller v. Shaw Indus., Inc.*, 167 F.3d 146 (3d Cir. 1999)). Dr. Lagana did none of this here.

**A. Dr. Lagana’s inability to define olmesartan-related sprue-like enteropathy, criteria for a diagnosis, or general causation establishes at the threshold that his methodology is unsound.**

Proof of general causation requires evidence to show “whether a substance is capable of causing *a particular injury or condition* in the general population.” *In re Zolofit (Sertralinehydrochloride) Prods. Liab. Litig.*, 176 F. Supp. 3d 483, 491 (E.D. Pa. 2016) (emphasis added); *Grant v. Bristol-Myers Squibb*, 97 F. Supp. 2d 986 (D. Ariz. 2000). As the *Grant* court explained, the plaintiffs’ experts attributed her claimed injuries to “a new undifferentiated atypical disease/syndrome associated with exposure to silicone in the silicone gel implants.” *Id.* at 989. The condition, however, was poorly defined; the experts’ “theory set forth various kinds of atypical connective tissue diseases, which allegedly manifest through a constellation of symptoms and are caused by an autoimmune response to silicone in breast implants.” *Id.* In other words—like the sprue-like enteropathy syndrome Dr. Lagana attempts to relate to olmesartan use here—the condition the plaintiffs’ experts attributed to silicone exposure could be



characterized by a wide array of non-specific symptoms and ailments that were grouped together by little more than the fact that the plaintiff experienced them after being exposed to a chemical.

In *Grant*, Bristol-Myers Squibb challenged these experts' opinions broadly, asserting that there was no reliable science to support the existence of a systemic disease caused by silicone exposure. The court agreed:

As a whole, the Court finds that the evidence regarding systemic disease as proposed by Plaintiffs' experts is not scientifically valid and therefore will not assist the trier of fact. As for the atypical syndrome that is suggested, where experts propose that breast implants cause a disease, but cannot specify the criteria for diagnosing the disease, it is incapable of epidemiological testing. This renders the experts' methods insufficiently reliable to help the jury.

*Id.* at 991.

Dr. Lagana admitted in his deposition that he could not specifically define the sprue-like enteropathy that he associates with olmesartan use, or provide a definition of the diagnostic criteria for this sprue-like enteropathy. He cannot even define general causation. With these shortcomings, Dr. Lagana's opinion is not scientifically valid.

**B. Dr. Lagana's Failure to Analyze the Bradford-Hill Criteria Also Precludes His General Causation Opinion.**

Dr. Lagana's failure to analyze the Bradford-Hill criteria provides equally compelling reason to exclude his general causation opinion. "In determining

whether an observed association between a chemical and a disease is causal (*i.e.*, general causation), scientists are guided by various factors, which are often referred to as the Hill criteria.” *Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F. Supp. 2d 584, 592–93 (D.N.J. 2002), *aff’d*, 68 F. App’x 356 (3d Cir. 2003). Bradford–Hill criteria “have been recognized for decades as a generally accepted methodological approach for determining causation in tort cases involving toxic exposure.” *In re Zoloft (Sertraline Hydrochloride) Prod. Liab. Litig.*, 26 F. Supp. 3d 466, 480 (E.D. Pa. August 2014).

The Bradford-Hill criteria “are nine factors widely used in the scientific community to assess general causation.” *See Gannon v. United States*, 292 F. App’x 170, 172–73 (3d Cir. 2008). “They are: (1) Strength of Association, (2) Consistency, (3) Specificity, (4) Temporality, (5) Biologic Gradient, (6) Plausibility, (7) Coherence, (8) Experimental Evidence, and (9) Analogy.” *Id.* at 173, n.1.

Experts who fail to analyze the Bradford-Hill factors in a scientifically reliable manner should be excluded. “While an expert need not consider or satisfy every criteria in order to reach a reliable causation opinion,” expert opinions should be excluded where an expert fails to consider the Bradford-Hill criteria as a whole. *See In re Zoloft (Sertraline Hydrochloride) Prod. Liab. Litig.*, 26 F. Supp. 3d 466, 480 (E.D. Pa. August 2014). “The Court cannot allow unscientific

speculation to be offered, even by genuinely talented scientists.” *Id.* at 481 (excluding expert testimony where the Court felt the experts focused on biological plausibility and did not adequately address “1) the strength of the association between maternal Zoloft exposure and birth defects in human infants; 2) the lack of replicated, statistically significant findings in the epidemiological literature; 3) the dose-response relationship, with attention to evidence regarding SSRI exposure at typical and maximum recommended clinical doses; and 4) alternative explanations for any associations between Zoloft exposure and birth defects in human babies (e.g. confounding factors).”). *See also, e.g., Dunn v. Sandoz Pharms. Corp.*, 672, 679 (M.D.N.C. 2003) (excluding expert whose “application of the Bradford-Hill criteria does not satisfy the reliability prong of *Daubert*”); *Caraker v. Sandoz Pharm. Corp.*, 172 F. Supp. 2d 1046, 1049 n.5 (S.D. Ill. 2001) (excluding causation expert whose Bradford-Hill analysis consisted largely of “curt conclusions making vast assumptions” and the analysis appeared to be an “afterthought” designed to justify the expert’s conclusions); *Soldo v. Sandoz Pharm. Corp.*, 244 F. Supp. 2d 434, 462, 514-28 (W.D. Pa. 2003).

Dr. Lagana’s report does not mention the Bradford-Hill criteria. He did not use the criteria in his report. When asked why he did not analyze those criteria, he testified that he did not know. The Bradford-Hill criteria are the only recognized system for determining whether an association between a chemical and a disease is

causative. *See In re Zoloft (Sertraline Hydrochloride) Prod. Liab. Litig.*, 26 F. Supp. 3d at 480. Dr. Lagana's failure to use the Bradford-Hill criteria, a failure he cannot explain, deems his general causation opinion unsound and ungrounded in any reliable scientific methodology.

### **CONCLUSION**

For the foregoing reasons, Defendants respectfully submit Dr. Lagana's general causation opinion should be excluded.

Respectfully submitted,

s/ Susan M. Sharko

Susan M. Sharko, Esq.

Michael C. Zogby, Esq.

Daniel B. Carroll, Esq.

DRINKER BIDDLE & REATH LLP

*A Delaware Limited Liability Partnership*

600 Campus Drive

Florham Park, New Jersey 07932-1047

(973) 549-7000

Attorneys for Defendants Daiichi Sankyo, Inc., Daiichi Sankyo US Holdings, Inc., Daiichi Sankyo Company, Ltd., Forest Laboratories, LLC, Forest Pharmaceuticals, Inc., and Forest Research Institute, Inc.

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